L4: Entry 7 of 35 File: USPT Mar 27, 2001

DOCUMENT-IDENTIFIER: US 6207147 B1
TITLE: Cancer immunotherapy using tumor cells combined with mixed lymphocytes

DATE FILED (1):
19971010

Abstract Text (1):
This invention comprises cellular vaccines and methods of using them in cancer immunotherapy, particularly in humans. The vaccines comprise stimulated lymphocytes allogeneic to the subject being treated, along with a source of tumor-associated antigen. The allogeneic lymphocytes can be stimulated by combining or coculturing them with leukocytes obtained from the subject to be treated or from another third-party donor. Tumor antigen may be provided in the form of primary tumor cells, tumor cell lines or tumor extracts prepared from the subject. Stimulated allogeneic lymphocytes and tumor antigen are combined and administered at a site distant from the primary tumor, in order to prime or boost a systemic cellular anti-tumor immune response. This approach overcomes the natural refractory nature of the immune system to stimulation by tumor antigens, generating a host response and potentially improving the clinical outcome.

Brief Summary Text (6):
An emerging area of cancer treatment is immunotherapy. The general principle is to confer upon the subject being treated an ability to mount what is in effect a rejection response, specifically against the malignant cells. There are a number of immunological strategies under development, including: 1. Adoptive immunotherapy using stimulated autologous cells of various kinds; 2. Systemic transfer of allogeneic lymphocytes; 3. Intra-tumor implantation of immunologically reactive cells; and 4. Vaccination at a distant site to generate a systemic tumor-specific immune response.

Brief Summary Text (7):
The first of the strategies listed above, adoptive immunotherapy, is directed towards providing the patient with a level of enhanced immunity by stimulating cells ex vivo, and then readministering them to the patient. The cells are histocompatible with the subject, and are generally obtained from a previous autologous donation.

Brief Summary Text (14):
The second of the strategies for cancer immunotherapy listed earlier is adoptive transfer of allogeneic lymphocytes. The rationale of this experimental strategy is to create a general level of immune stimulation, and thereby overcome the anergy that prevents the host's immune system from rejecting the tumor. Strausser et al. (1981) J. Immunol. Vol. 127, No. 1 describe the lysis of human solid tumors by autologous cells sensitized in vitro to alloantigens. Zarling et al. (1978) Nature 274:269-71 demonstrated human anti-lymphoma responses in vivo following sensitization with allogeneic leukocytes. Kondo et al. (1984) Med Hypotheses 15:241-77 observed objective responses of this strategy in 20-30% of patients, and attributed the effect to depletion of suppressor T cells. The studies were performed on patients with disseminated or circulating disease. Even though these initial experiments were conducted over a decade ago, the strategy has not gained general acceptance, especially for the treatment of solid tumors.

Brief Summary Text (15):
The third of the immunotherapy strategies listed earlier is intra-tumor implantation. This is a strategy directed at delivering effector cells directly to the site of action. Since the transplanted cells do not circulate, they need not be histocompatible with the host. Intratumor implantation of allogeneic cells may promote the ability of

L17 ANSWER 2 OF 7 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1998016556 MEDLINE
DOCUMENT NUMBER: 98016556 PubMed ID: 9354936
TITLE: Oxidants differentially regulate the **heat shock** response.
AUTHOR: Wallen E S; Buettner G R; Moseley P L
CORPORATE SOURCE: Department of Internal Medicine, University of New Mexico, Albuquerque 87131-5271, USA.
SOURCE: INTERNATIONAL JOURNAL OF HYPERTHERMIA, **(1997 Sep-Oct)** 13 (5) 517-24.
Journal code: 8508395. ISSN: 0265-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971209

AB Cells, animals, and humans respond to hyperthermia through the synthesis of a family of proteins termed **heat shock** proteins (**HSPs**). Because hyperthermic stress may also result in **mitochondrial uncoupling** and the generation of reactive oxygen species, we wondered whether oxidant stress was sufficient to increase cellular levels of **HSP70**. **HSP70** was detected in cells heated or treated with menadione but not in those treated with hydrogen peroxide or xanthine/xanthine oxidase. We speculate that oxidant stress from menadione exposure is qualitatively different from exposure from hydrogen peroxide or xanthine/xanthine oxidase.

the transplanted cells to react with the tumor, and initiate a potent graft versus tumor response.

Brief Summary Text (18):
The fourth of the immunotherapy strategies listed earlier is the generation of an active systemic tumor-specific immune response of host origin. The response is elicited from the subject's own immune system by administering a vaccine composition at a site distant from the tumor. The specific antibodies or immune cells elicited in the host as a result will hopefully migrate to the tumor, and then eradicate the cancer cells, wherever they are in the body.

Detailed Description Text (3):
The strategy is a significant departure from previous approaches to cancer immunotherapy in humans. Stimulated lymphocytes have been used in experimental human therapy, but as part of adoptive therapy--the lymphocytes were originally obtained from the subject or a closely matched donor. In this invention, the stimulated lymphocytes are allogeneic to the subject. The stimulated lymphocytes provide a potent immunostimulation that elicits a response against simultaneously injected tumor associated antigen. As a result, a cellular immune response emerges that is specific for the tumor, and much stronger than can be achieved by simply administering the patent's tumor cells, or a derivative thereof.

Detailed Description Text (103):
A second group of suitable subjects is known in the art as the "adjuvant group". These are individuals who have had a history of cancer, but have been responsive to another mode of therapy. The prior therapy may have included (but is not restricted to) surgical resection, radiotherapy, traditional chemotherapy, and other modes of immunotherapy. As a result, these individuals have no clinically measurable tumor by the definition given above. However, they are suspected of being at risk for recurrence or progression of the disease, either near the original tumor site, or by metastases. The adjuvant group may be further subdivided into high-risk and low-risk individuals. The subdivision is made on the basis of features observed before or after the initial treatment. These features are known in the clinical arts, and are suitably defined for each different cancer. Features typical of high risk subgroups are those in which the tumor has invaded neighboring tissues, or which show involvement of lymph nodes.

Detailed Description Text (114):
The pharmaceutical compositions of this invention may be given following, preceding, in lieu of, or in combination with, other therapies relating to generating an immune response or treating cancer in the subject. For example, the subject may previously or concurrently be treated by chemotherapy, radiation therapy, and other forms of immunotherapy and adoptive transfer. Where such modalities are used, they are preferably employed in a way or at a time that does not interfere with the immunogenicity of the compositions of this invention. The subject may also have been administered another vaccine or other composition in order to stimulate an immune response. Such alternative compositions may include tumor antigen vaccines, nucleic acid vaccines encoding tumor antigens, anti-idiotype vaccines, and other types of cellular vaccines, including cytokine-expressing tumor cell lines.

Detailed Description Text (125):
Nine patients with biopsy proven high grade astrocytomas (Daumas-Duport grade III or IV) were randomly selected for intratumoral implantation of MLC-activated allogeneic lymphocytes following recurrence or progression of their astrocytomas after standard therapies. The trial was approved by the Institutional Review Board of the Hospital of The Good Samaritan, Los Angeles, Calif. All patients were enrolled with informed consent. Patient ages ranged from 24 to 67 years (mean 50 years) and there were 4 males and 5 females. Eight patients had grade IV astrocytoma (glioblastoma multiforme, GBM) and one patient had grade III astrocytoma (anaplastic astrocytoma). All patients had failed prior debulking surgeries, radiation therapy, chemotherapy, and immunotherapy (autologous LAK cells plus IL-2), and presented with progressively growing tumor. Karnofsky performance scores ranged from 60 to 80 (mean 72.6) at the time of immunotherapy. Patient characteristics are listed in Table 1:

Detailed Description Text (128):
Clinical toxicities associated with intratumoral implants of MLC-activated allogeneic lymphocytes are documented in Table 2. At each dosage level, some patients experienced grade 1 and grade 2 toxicities. However, these were transient effects, and it is unclear whether these were effects of the immunotherapy or surgical reaction. The degree of cerebral edema at each dosage level was controlled by administration of

moderate doses of dexamethasome (between 8 and 24 mg/day), which was maintained for up to several months.

Detailed Description Text (130):
Clinical responses were evaluated by three criteria: a) serial MRI scans, using contrast enhancement with triaxial measurements of maximal enhancing diameter; b) Karnofsky performance scores; and c) survival. Tumor volumes from serial MRI scans for the 9 patients enrolled in the trial are shown in FIG. 1. MRI evidence of tumor response to the alloimplant (as assessed by gadolinium enhanced, T1 weighted MRI images) was seen in 3 of 9 patients. There was complete tumor regression in two patients and partial tumor regression (>50% shrinkage) in one patient over a 10 to 130 week observation period. In five patients, serial MRI scans showed stabilization of tumor size, with essentially no tumor growth over an 8 to 20 week observation period.

Detailed Description Text (131):
Only one patient showed progressive tumor growth after alloimplantation. The overall mean survival for the patients at each dosage level measured from the time of immunotherapy was 24 weeks at 2.times.10.sup.9 cells (range 18-24 weeks), 64 weeks at 4.times.10.sup.9 cells (range 10-135 weeks), and 72 weeks at 6.times.10.sup.9 cells (20-140 weeks). Importantly, there were two long term survivors; one at the 4.times.10.sup.9 cell dosage (BTP-006, >125 weeks), and one at the 6.times.10.sup.9 cell dosage (BTP-008, >135 weeks).

Detailed Description Text (133):
Each of these patients were upgraded in their Karnofsky performance scores from 80- (preimplant) to 100. Two patients are currently alive and enjoying a good quality of life. Serial MRI scans of patient BTP-006 indicated continued tumor regression over a 24 month period. Serial MRI scans of patient BTP-008 also indicated a slow, persistent reduction in tumor size over a 24 month observation period.

Detailed Description Paragraph Table (1):
TABLE 1 Therapies Patient Age Sex Dx* Site** Prior to Study*** KPS**** BTP-001 67 m AA LTL RT, CT, GK 80 (4 mo) BTP-002 53 f GBM LFL RT, GK (0.5 mo) 70 BTP-003 40 m GBM RTL GK, RT, CT, GK, 70 ITx, GK (0.5 mo) BTP-004 45 f GBM RTL DBS, RT, CT, 60 RT, GK (2 mo) BTP-005 61 m GBM LOL DBS, RT, GK, 70 GK (0.5 mo) BTP-006 24 f GBM ROL CT, GK (7 mo) 80 BTP-007 56 m GBM LTL RT, DBS, CT, 70 GK (1.5 mo) BTP-008 48 f GBM LOL RT, CT, GK 80 (0.5 mo) BTP-009 51 f GBM RPL DBS, RT, CT, 70 GK (0.5 mo) *GBM = Glioblastoma Multiforme (astrocytoma, Daumas-Duport Grade IV); AA = Anaplastic Astrocytoma (astrocytoma, Daumas-Duport Grade III). **LFL = Left Frontal Lobe; RFL = Right Frontal Lobe; RPL = Right Parietal Lobe; LTL = Left Temporal Lobe; ROL = Right Occipital Lobe; LOL = Left Occipital Lobe. ***DBS = Debulking Surgery; RT = External Beam Radiation Therapy; CT = Chemotherapy; ITx = Prior Immunotherapy (LAK cells + IL-2); GK = Gamma Knife Therapy (months prior to alloimplant). ****KPS = Karnofsky Performance Score (at time of immunotherapy).

Detailed Description Paragraph Table (3):
TABLE 3 Patient Survival* I.D. Cell Dosage Toxicities Observed (weeks) Response** BTP-001 2 .times. 10.sup.9 Grade 1 77 SD BTP-002 2 .times. 10.sup.9 Grade 2 31 PR BTP-003 2 .times. 10.sup.9 Grade 1 113 SD BTP-004 4 .times. 10.sup.9 Grade 2 75 SD BTP-005 4 .times. 10.sup.9 Grade 1 75 SD BTP-006 4 .times. 10.sup.9 Grade 2 184+ CR BTP-007 6 .times. 10.sup.9 Grade 2 130 SD BTP-008 6 .times. 10.sup.9 Grade 2 160 + CR BTP-009 6 .times. 10.sup.9 Grade 2 48 PD *Survival (in weeks) from time of initial diagnosis. + indicates currently live patients. **Response to immunotherapy. CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Other Reference Publication (5):
Dillman et al., "Establishing in vitro cultures of autologous tumor cells for use in active specific immunotherapy" J. Immunother. (1993) 14:65-69.

Other Reference Publication (9):
Kondo et al., "Rationale for a novel immunotherapy of cancer with allogeneic lymphocyte infusion" Med. Hypotheses (1984) 15:241-277.

Other Reference Publication (15):
Lillehei et al., "Long-term follow-up of patients with recurrent malignant gliomas treated with adjuvant adoptive immunotherapy" Neurosurgery (1991) 28:16-23.

Other Reference Publication (16):

Mitchell et al., "Active specific immunotherapy of melanoma with allogeneic cell lysates. Rationale, results, and possible mechanisms of action" Ann. N.Y. Acad. Sci. (1993) 690:153-166.

Other Reference Publication (18):
Rosenberg et al., "Gene transfer into humans--Immunotherapy of patients with advanced melanoma, using tumor-infiltrating lymphocytes modified by retroviral gene transduction" New Engl. J. M. ed. (1990) 323:570-578.

Other Reference Publication (22):
Schirrmacher et al., "Workshop: Active specific immunotherapy with tumor cell vaccines" J. Cancer Res. Clin. Oncol. (1995) 121:487-489.

WEST

End of Result Set

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L5: Entry 1 of 1 File: USPT Nov 17, 1998

US-PAT-NO: 5837233
DOCUMENT-IDENTIFIER: US 5837233 A

TITLE: Method for treating tumors

DATE-ISSUED: November 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Granger; Gale A.	Laguna Beach	CA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
University Of California	Oakland	CA			02

APPL-NO: 08/ 616880 [PALM]
DATE FILED: March 15, 1996

PARENT-CASE:
This application is a continuation-in-part of U.S. patent application Ser. No. 08/406,388, filed Mar. 17, 1995.

INT-CL: [06] A61 K 48/00, C12 N 5/00

US-CL-ISSUED: 424/93.1; 424/93.2, 435/375
US-CL-CURRENT: 424/93.1; 424/93.2, 424/93.21, 435/375

FIELD-OF-SEARCH: 435/320.1, 435/240.2, 435/240.21, 424/93.21, 424/277.1, 424/9.1, 424/93.3

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4038145	July 1977	Devlin	195/103.5
☐	4677056	June 1987	Dupont et al.	435/7
☐	5057423	October 1991	Hiserodt et al.	435/240.23
☐	5308626	May 1994	Landucci et al.	424/93
☐	5382427	January 1995	Plunkett et al.	424/85.2
☐	5484596	January 1996	Hanna, Jr. et al.	424/277.1

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO 95/31107	November 1995	WO	

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murine tumor be allosensitization" Cancer Immunol. Immunother. (1984) 17:117-123.
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Appendix A: Curriculum vitae of Gale A. Granger.
Appendix B (item 1): E.W.B. Jeffes et al. Therapy of recurrent high grate gliomas with surgery, and autologous mitogen activated IL-2 stimulated killer (MAK) lymphocytes . . . J. Neuro-Oncol. 15:141-155, 1993.
Appendix B (item 2): R.S. Yamamoto et al. Basical and clinical studies with intratumor immonotherapy of gliomas with alloimmune lymphoid cells. Poster presentation, American Association of Neurological Surgeons.
Appendix B (item 3): G. Ioli et al. "Basic & clinical studies with intratumor immunotherapy of gliomas with allogeneic lymphoid cells" Proc. Amer. Assoc. Cancer Res. (Mar. 1994) 35:518 (Abstract 3088).
Appendix B (item 4): G. Granger et al. "Basic and clinical studies of intralesional therapy of gliomas with allogeneic lymphoid cells" Proc. Amer. Assoc. Cancer Res. (Mar. 1995) 36:472 (Abstract 2812).
Appendix C: Letters regarding Gifts from Good Samaritan Hospital to support research of Gale A. Granger; Table of Gifts.
Appendix D: List of patients treated according to the invention up to Sep. 26, 1996.
Appendix E: Break-down of charges for alloactivated donor cells produced at U.C.I.
Protocol 1 (item 1): Phase I trial for brain cancer, Good Samaritan Hospital. Protocol version originally filed with the IRB at the Good Samaritan Hospital.
Protocol 1 (item 2): Phase I trial for brain cancer, Good Samaritan Hospital. Protocol version as subsequently amended to cover 20 patients.
Protocol 1 (item 3): "Informed Consent Form" (Patient).
Protocol 2 (item 1): Phase I trial for brain cancer, Long Beach Memorial Hospital.
Protocol 2 (item 2): "Consent to Act as a Research Subject" (Donor).
Protocol 2 (item 3): "Consent to Act as a Research Subject" (Patient).

Protocol 3 (item 1): Phase I trial for metastatic melanoma, U.C.I. Medical Center.
Protocol 3 (item 2): "Consent to Act as a Human Research Subject" (Donor).
Protocol 3 (item 3): "Consent to Act as Human Research Subject" (Patient).
Protocol 4 (item 1): Phase I trial for pancreatic canter, U.C.I. Medical Center.
Protocol 4 (item 2): "Consent to Act as a Human Research Subject" (Patient).
Protocol 4 (item 3): "Consent to Act as a Human Research Subject" (Donor).
Protocol 5 (item 1): Phase I trial for bladder & prostate cancer, U.C.I. Medical Center.
Protocol 5 (item 2): "Consent to Act as a Human Research Subject" (Patient).
Protocol 5 (item 3): "Consent to Act as a Human Research Subject" (Donor).
Protocol 6: Phase II trial for brain cancer, Good Samaritan Hospital.
Protocol 7: Phase II trial for brain cancer, U.C.I. Medical Center.
Declaration by John C. Hiserodt regarding Human Clinical Trials.
Appendix F: Curriculum vitae of John C. Hiserodt.
Appendix G: "Immunotherapy for recurrent high grade gliomas: I. A pilot study using intratumoral implants of MLC-activated allogeneic lymphoid cells for the treatment of recurrent malignant astrocytomas" by J.C. Hiserodt, S. Jacques, C. Dumas, and G.A. Granger. [Unpublished manuscript] .

ART-UNIT: 162

PRIMARY-EXAMINER: Chambers, PHD.; Jasemine C.

ASSISTANT-EXAMINER: Hauda; Karen M.

ABSTRACT:

A method is provided for treatment of a mammalian patient having a tumor by administering to the patient allogenic donor lymphocytes that have been co-cultured in the presence of the patient-derived lymphocytes under conditions sufficient to alloactivate the donor lymphocytes. It is preferred that the donor lymphocytes be introduced intralesionally. This method is preferred for treatment of glioblastoma in humans.

37 Claims, 2 Drawing figures

L20 ANSWER 71 OF 237 MEDLINE DUPLICATE 44

ACCESSION NUMBER: 89354273 MEDLINE
DOCUMENT NUMBER: 89354273 PubMed ID: 2766276
TITLE: Mechanism of transport and intracellular binding of porfiromycin in HCT 116 human colon carcinoma cells.
AUTHOR: Pan S S; Johnson R; Gonzalez H; Thohan V
CORPORATE SOURCE: University of Maryland Cancer Center, Baltimore 21201.
CONTRACT NUMBER: CA33697 (NCI)
SOURCE: CANCER RESEARCH, **(1989 Sep 15)** 49 (18) 5048-53.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198910
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19970203
Entered Medline: 19891003

AB The mechanism of uptake and efflux of porfiromycin (PFM) by HCT 116 human colon carcinoma cells or freshly obtained human RBC was investigated. The time course of uptake of radioactivity upon exposure of HCT 116 cells to [14C]PFM showed one fast and one slow phase of linear increase. The initial phase of PFM uptake was not saturable with external drug concentrations from 2 to 100 microM. PFM accumulation was temperature dependent with a temperature coefficient (Q10 24-37 degrees C) of 2.3 +/- 0.3. PFM uptake was not affected either by individual inhibitors such as 1 mM 2,4-**dinitrophenol**, sodium azide, iodoacetic acid, ouabain, 0.02 mM oligomycin, p-hydroxylmercuribenzoate, 0.2 mM N-**ethylmaleimide**, or by combinations of inhibitors. PFM uptake did not demonstrate competitive inhibition by unlabeled PFM and mitomycin C. Efflux of cellular radioactivity was not affected by the above mentioned inhibitors or by verapamil, diltiazem, or trifluoperazine. Only aliphatic **alcohols** accelerated the initial influx rate. The RBC, however, only exhibited the initial fast accumulation of [14C]PFM, and all the 14C accumulated by RBC was exchangeable. These data demonstrate that the uptake and the efflux of PFM in HCT 116 cells and RBC comprise a passive diffusion process.